INTRAVITREAL TRIAMCINOLONE AND ITS EFFECT ON INTRAOCULAR PRESSURE

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CERTIFICATE

This is to certify that this dissertation entitled **"INTRAVITREAL TRIAMCINOLONE AND ITS EFFECT ON INTRAOCULAR PRESSURE"** submitted for MS (Branch III) Ophthalmology March 2007, The Tamil Nadu Dr. MGR Medical University, is a bonafide work done by **Dr. N. Vidhya,** under our guidance and supervision in the Glaucoma Department of Aravind Eye Care System and Postgraduate Institute of Ophthalmology, Madurai during her residency period from May 2004 to April 2007.

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INTRODUCTION

Periocular and Orbital injections of long-acting corticosteroids are being used to treat inflammatory conditions of the eye for many years[1, 2] . However it has been suggested that peribulbar injection may not be adequate to treat chronic ocular disease because their action is partly due to systemic absorption of the drug and their effectiveness lasts only for a few days to weeks[3]. Intraocular administration has the potential to deliver steroids at high local concentrations

The safety of intravitreal steroid preparations has been studied in animal models. Dexamethasone has been shown to be safe in both primates and humans. Doses of up to 1 mg were well tolerated in rabbits and caused no permanent changes in the ERG or the retinal histology. However Dexamethasone sodium phosphate is soluble and has a short half life of about 3 days[4,5]. In contrast triamcinolone acetonide is hydrophobic and appears to provide therapeutic levels in the vitreous for up to 3 months[6]. Based on experimental studies by Machemer and coworkers[7,8] and other researchers, intravitreal triamcinolone acetonide has increasingly been used as treatment for intraocular proliferative, edematous, and neovascular diseases. Intravitreal triamcinolone has recently been shown to be nontoxic to the human retina and well tolerated[9,10]. It has shown promising results in uveitic[11] and

pseudophakic[12] cystoid macular edema resistant to other treatments and also in resolving exudative retinal detachments in Vogt Koyanagi Harada syndrome[13]. Efficacy has also been reported in cystoid Macular edema caused by central retinal vein occlusion[14], ischemic branch retinal vein occlusion[15] and diabetic maculopathy[17].

Despite good initial anatomical and functional visual response to intravitreal triamcinolone when used in these conditions, macular edema has been reported to recur following treatment, often necessitating repeated injections[15]. The efficacy in age related macular degeneration is not very clear[16]. An antiangiogenic effect has been noted, but the gain in visual acuity has not been very impressive[18]. Danis et al. , however noted a short-term improvement in visual acuity and fundus findings in exudative macular degeneration following intravitreal injection of 4mg of triamcinolone acetonide[19].

As the applications of triamcinolone expand, there is a growing interest in the safety of corticosteroid injections[20]. There does not appear to be much, if any of demonstrable toxicity after intravitreal injection of triamcinolone[21]. Side effects however appear in the long term. The major side effects include procedure-related side effects (e.g. pain etc), steroid-induced intraocular pressure rise, cataract, vascular occlusions[21], pseudohypopyon[22], infectious and non-infectious endophthalmitis[23]. An incidence of 15-20% of clinically

significant cataract that eventually underwent cataract surgery has been reported within a year of intravitreal injection of triamcinolone acetonide[24]. An incidence of 26.2% cataract surgery has been reported by Cekic et al[25].

Noninfectious endophthalmitis and pseudohypopyon probably represent dispersion of triamcinolone crystals in the vitreous and the anterior chamber. The incidence has been reported to range from 0.2% to 1.6%. The majority resolve spontaneously[22]. Nevertheless such cases need to be kept under close observation.

A rise in the intraocular pressure is among the most serious of side effects. Jonas reported an incidence of 50% of eyes starting 1 to 2 months after an intravitreal injection of 25mg of triamcinolone acetonide[27]. Bakri et al , noted an IOP rise in 48.8% with high levels reached in 27.9%. The mean time to reach the peak IOP was 6.6 weeks. These levels were noted to be higher than those reported for topical and posterior sub-Tenon steroids[26]. While all patients in Bakri's study had pressures reversed by medication, intractable glaucoma has also been reported[28, 29.]. These cases needed to be further treated with either a filtering surgery or vitrectomy with removal of the intravitreal steroid.

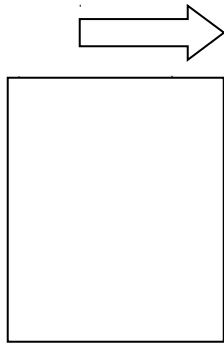
Smithen et al, in a study of 89 patients found that the peak IOP rise was reached a mean of 96.7days from the intravitreal injection. They also noted that the slope of survival plot curves did not flatten with increasing follow-up, which meant that the patients may be at risk for pressure elevations for a prolonged period of time[30].

Triamcinolone acetonide has been noted to provide therapeutic levels in the vitreous for about three months[6, 9]. Because the durations of effects and side effects may outlast the intraocular availability, a closer follow up of these patients is needed to detect an IOP rise[31]. A follow up time of 6 months has been fixed for our study.

HISTORICAL PERSPECTIVE

Intravitreal injection has been used in the treatment of human ocular disease for nearly a century. Initially reported in 1911 by Ohm[32], as a means to introduce air for retinal tamponade and repair of detachment, the intravitreal administration of pharmaceutical agents was pioneered in the mid 1940's with the use of penicillin to treat endophthalmitis

Blankenship et al[62], demonstrated in 1991, that Dexamethasone was well tolerated but of no therapeutic value for post vitrectomy treatment of diabetic retinopathy. In 1995, Penfold et al,[16] in a pilot study demonstrated that triamcinolone acetonide; a longer acting corticosteroid was well tolerated in patients with exudative ARMD. From that time onwards, intravitreal triamcinolone acetonide as an ophthalmic tool is gaining rapid popularity and acceptability among physicians in treating conditions such as macular edema, choroidal neovascularization.



The ease of delivery, ease of availability besides the promise of success makes it both a potential sight saver and also a much inappropriately overused modality with devastating complications. Hence an investigation into the safety and efficacy of intravitreal triamcinolone of intravitreal triamcinolone is much needed

REVIEW OF LITERATURE

Studies on intravitreal triamcinolone injection

1. Cardillo JA et al.,in his study on Comparison of intravitreal versus posterior sub-Tenon's capsule injection of triamcinolone acetonide for diffuse diabetic macular edema states that intravitreal and Sub-Tenon's capsule injections of triamcinolone acetonide may be equally tolerated, with short-term performance clearly favoring the intravitreal (4 mg) more than the SBT capsule (40 mg) route for the anatomic and functional aspects of improvement tested in this investigation.and intravitreal injection did not show any significant rise in IOP. (Ophthalmology. 2005 ;112:1557-63).
2. Jonas JB in his study on Intravitreal triamcinolone acetonide for treatment of intraocular proliferative,exudative, and neovascular diseases concluded that complications of intravitreal triamcinolone therapy include secondary ocular hypertension in about 40% of the eyes injected, cataractogenesis, postoperative infectious and non-infectious endophthalmitis, and pseudo-endophthalmitis and Intravitreal triamcinolone acetonide may offer a possibility for adjunctive treatment of intraocular edematous and neovascular

disorders. The duration of the effect of a single intravitreal injection of triamcinolone depended on the dosage given. Given in a dosage of about 20mg to non-vitrectomized eyes, the duration of the effect and of the side-effects was 6-9 months (Prog Retin Eye Res. 2005 ;24:587-611).

3. Ozkiris A et al., after analyzing the complications of intravitreal triamcinolone given for various reasons had concluded that the most common complication encountered during follow-up was transient elevation of IOP above 21mmHg (20.8%) and The mean IOP values at 1, 3 and 6 months were statistically significantly higher than the mean preinjection value ($p < 0.001$).(Can J Ophthalmol. 2005 ; 40:63-8).
4. Jonas JB et al., in his analysis after intravitreal injection of 20mg of tricort found that Mean IOP started to rise 1 week after injection and returned to baseline values approximately 8 to 9 months after injection. Younger age ($P = 0.029$) was significantly associated with triamcinolone-induced ocular hypertension.Triamcinolone responders and triamcinolone nonresponders did not vary significantly in gender ($P = 0.42$), refractive error ($P = 0.86$), diabetes mellitus status ($P = 0.74$), and reason for treatment(Ophthalmology. 2005 ;112:593-80).

5. Ozkiris A et al., evaluated the effectiveness of intravitreal triamcinolone acetonide as primary treatment of macular edema in branch retinal vein occlusion and compared with patients who had received laser treatment found that the mean edema map value of Group 1 significantly decreased by 40% at 6-month examinations when compared with preinjection value($p<0.001$). In Group 1, mean increase in intraocular pressure elevation was 19.8%at the 1-month, 26.9% at 3-month, and 5.7% at 6-month visits, but intraocular pressures were under control with topical antiglaucomatous medications.(Eur J Ophthalmol.2005;15:96-101).

6. Smithen LM et al., analyzed the incidence of intraocular pressure (IOP) elevation following intravitreal triamcinolone injection and concluded that IOP elevation after intravitreal triamcinolone injection is common and may take an extended period of time to manifest. The proportion of patients who developed a pressure elevation to atleast 24 mm Hg was much higher for those with baseline IOP 15 mm Hg or greater. (Am J Ophthalmol. 2004 ;138:740-3).

7. Gillies MC et al., determined the safety of a single intravitreal injection of triamcinolone acetonide (4 mg) in patients with subfoveal choroidal neovascularization caused by age-related macular degeneration and found that Triamcinolone-treated eyes had a significantly increased risk of developing mild or moderate elevation of the intraocular pressure. Topical glaucoma medication reduced intraocular pressure to acceptable levels in all patients. There was significant progression of cataract in the triamcinolone-treated eyes.(Arch Ophthalmol. 2004 ; 122:336-40).

8. Bakri SJ et al., in his study on The effect of intravitreal triamcinolone acetonide on intraocular pressure concluded that A single 4-mg intravitreal triamcinolone acetonide injection is associated with an increase in IOP of 10 mm Hg or greater in 27.9% of eyes after the first injection. All eyes responded to topical glaucoma medication. (Ophthalmic Surg Lasers Imaging. 2003 ;34:386-90).

9. Wingate RJ et al., in his study on intravitreal triamcinolone and intraocular pressure concluded that Approximately 30% of the study group developed a significant rise (> or =5 mm Hg) in intraocular

pressure above baseline during the first 3 months. (Aust N Z J Ophthalmol. 1999;27:431-2).

10. Khairallah M et al ., in his study on Primary intravitreal triamcinolone acetonide for diabetic massive macular hard exudates found that Intravitreal injection of triamcinolone acetonide appears to be beneficial for reducing hard exudates, decreasing fluorescein leakage, and significantly improving visual acuity in patients with diabetic massive hard exudates. Visual improvement may not be important due to profound anatomical impairment caused by hard exudates deposition. Intraocular pressure elevation occurred in 25% and was successfully treated by topical medication (Retina. 2005;25:835-9)

PHARMACOLOGY

Triamcinolone acetonide is a potent, relatively insoluble steroid that has been used for treatment of ocular inflammation by peribulbar or sub-tenon's injection for decades[3] Intravitreal administration of the drug offers the potential to deliver corticosteroids at high local concentrations for extended periods. Studies have suggested that Periocular administration may not be adequate for chronic ocular diseases. Part of the effect is due to systemic absorption of the drug. Also the therapeutic effectiveness lasts only for a few days to weeks[3].

Recently Cardillo et al., noted that intravitreal triamcinolone yielded superior results when compared with posterior sub-tenon's injection at 1 month and 3 months with respect to macular thickness and visual acuity[32].

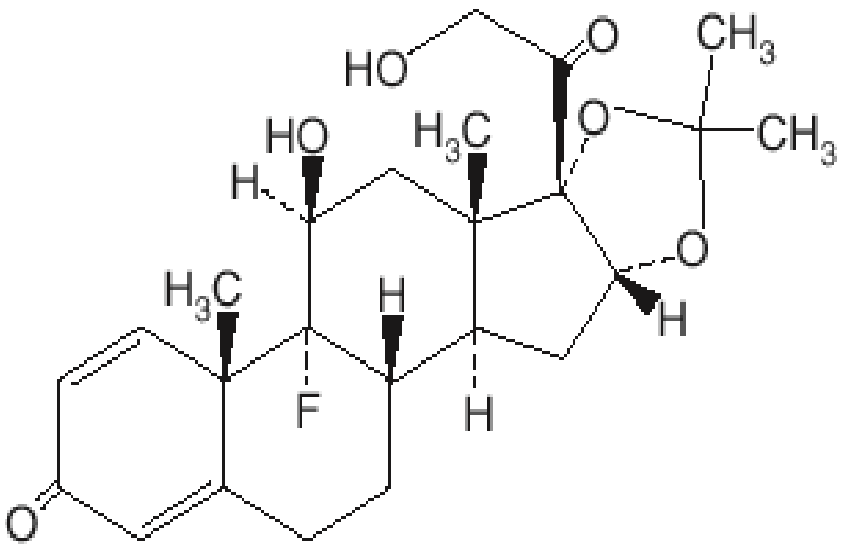
Conway et al.,[12] reported benefit with intravitreal injections of triamcinolone in patients who were resistant to topical and Periocular steroid injections. It is possible that these are dose-related phenomena with intravitreal steroids delivering higher concentrations to the retina[12].

The physical and biochemical properties of triamcinolone acetonide make it the ideal drug for intravitreal injections.

The physical properties:

1. Water insoluble
2. Particulate.
3. Visible.
4. Non toxic
5. Longer retention time.

Chemical structure of Triamcinolone Acetonide:



PHARMACOKINETICS

The study on the pharmacokinetics of the intravitreal steroid gives an insight to the possible duration of the therapeutic effect. Drug concentrations in the vitreous is determined not only by the amount of drug given, but also by the distribution and clearance of such compounds. The pharmacokinetic characteristics depend on the anatomical and physiological features at the site of administration and the physiochemical properties of the agent administered. Little is known about the effect of age on the disposition of compounds administered directly into the vitreous.

Studies on pharmacokinetics:

Schindler and co-workers [34] evaluated the clearance rate of intravitreal triamcinolone acetonide injection in a rabbit model by performing both ophthalmoscopy and colorimetric tests to determine the clearance of 0.5 mg of drug injected into rabbit eyes that underwent no surgery, vitrectomy, or vitrectomy combined with lensectomy. They found that in eyes that had no surgery the drug persisted for a long period.

Scholes et al[35]., in their animal experiment found out that the ophthalmoscopic presence of white crystals of triamcinolone may not correlate with therapeutic triamcinolone acetonide levels.

The human study done by Beer et al.[36], concluded that the mean elimination for nonvitrectomised eyes was 18.6 days while for vitrectomised eyes was only 3.2 days. Given the calculated half- life, a single 4 mg intravitreal injection of triamcinolone could be expected to last approximately three months in a non vitrectomised eye.

Neither study attempted to identify the route of elimination of the drug from the eye or the level of the compound that could be achieved in various compartments after intravitreal injection. The possibility for rapid elimination in vitrectomised subjects could be surgically induced changes affecting elimination via the anterior or posterior routes or the differences in the rates of triamcinolone crystal dissolution resulting from the free flow in the vitreous cavity not present in the absence of surgery .

DURATION OF ACTION

After a single intravitreal injection of 25mg, triamcinolone acetonide was detected in low, but measurable concentrations up to 1.5 years in aqueous samples. No difference between phakic and pseudophakic patients was found. No correlation with the specific retinal disease status was found either[30]. Triamcinolone acetonide crystals can remain visible in the eye at least up to 9 months after the injection[37]. Beer and associates noted a mean elimination half life of 18.6 days after an intravitreal injection of 4 mg in nonvitrectomised eyes which means that measurable concentrations would be expected to last for approximately 3 months[36]. Thus it appears that there is dose dependant retention in the vitreous cavity with higher doses being retained for longer periods[30]. Therapeutic levels appear to be present in the vitreous for about three months[6, 38]

Safety of an intravitreal injection of triamcinolone :

Triamcinolone has been shown to be safe in monkeys and has no effect on the histopathology and electroretinogram in rabbit retina.[9,39] Hida et al., investigated the effects of the vehicles available in commercial preparations alone without the steroid. They found the vehicle to be devoid of toxic effects[40]. In humans, injections of up to 25mg of triamcinolone acetonide has been shown to be devoid of retinal toxicity in vitrectomised and nonvitrectomised eyes [9,40].

MECHANISM OF ACTION

Intravitreal steroids have shown promise in reducing inflammation in animal models of endophthalmitis, uveitis and proliferative vitreoretinopathy and have been used in pilot studies in humans and could therefore, be of potential use in refractory uveitis[4, 6,11].

Corticosteroids inhibit prostaglandin and leukotriene synthesis by inhibiting phospholipase A, thereby inducing an anti-inflammatory effect[41]. Furthermore they reverse capillary permeability, stabilize blood vessels and the blood-retinal barrier[42-49] thereby also reducing exudation[45] and inhibit the expression of inflammatory adhesion molecules[46].

Many corticosteroids have been shown to be potent inhibitors of neovascularization in animal models and are among the most potent antiangiogenic agents known [5, 19]. The mechanism of steroid angioinhibition has been shown to be an effect on vascular endothelial cell extra cellular matrix turnover as well as inhibition of inflammatory cells, which invariably precipitate an inflammatory response [47,48].

It is however possible that the usual mechanisms alone may not be at work when an intravitreal injection is given.[34] In this situation the doses used are far in excess of those necessary to activate corticosteroid receptors and

also include inhibition of lipid per oxidation and hydrolysis that damages neuronal and micro vascular membranes after injury.[37] This may explain their efficacy in conditions that are otherwise resistant to conventional steroid administration[12].

The proposed mechanisms in macular edema include–

1. Increases the integrity of blood ocular barrier
2. Decreased capillary permeability
3. Decreases local availability of chemical mediators
4. Causes vasoconstriction of capillaries
5. Increased diffusion by modulation of Ca++ channel
6. Decreased VEGF
7. Decreases the cystic spaces

Triamcinolone acetonide modulates the permeability and adhesion of human choroidal endothelial cells in culture. Penfold et al[49]., demonstrated that cytokine induced expression of intracellular adhesion molecule -1 is down regulated by triamcinolone acetonide and interferon gamma induction of vascular permeability was decreased by triamcinolone acetonide.

Wang et al[50]., demonstrated that matrix metalloproteinase were down regulated following incubation with triamcinolone suggesting that the active

remodeling of the extra cellular matrix necessary for neovascularization can be inhibited.

Wilson et al[51]demonstrated that a single injection of triamcinolone can reduce the severity of blood –retinal barrier breakdown following pan retinal photocoagulation.

Sagamoto et al[52]., used triamcinolone acetonide as a surgical tool during pars plana vitrectomy for complex diabetic retinopathy and discovered that in the post operative period the blood ocular barrier was more preserved compared to eyes that underwent routine vitrectomy without intraoperative triamcinolone acetonide.

PROCEDURE OF INTRAVITREAL TRIAMCINOLONE INJECTION

The drug is commonly employed in a dose of 4mg injected in 0.1ml, though some have employed a dose of 25 mg injected in 0.1 ml[41]. The commercial preparation contains 40mg in 1ml with benzyl alcohol, carboxymethylcellulose and polysorbate 80 as vehicles. Most ophthalmologists would prefer to inject a vehicle free drug. The vehicle may be removed by the process of sedimentation and repeated washing of the precipitate with ringer lactate.

The disadvantage is that the process is not titrated and drug loss can occur while removing the supernatant. The final concentration of triamcinolone attained by such a process is not known. Nishimura et al devised a technique with the use of two syringe connected by a 3 way valve and 0.2 micron filters. The commercial preparation is pushed through the filter with no loss of drug and subsequently is reconstituted with saline pushed in though the second filter. Recently commercial preparations free of the vehicle have been made available (aurocort®).

Technique of Injection:

The procedure is to be done in the operation theatre with all aseptic precautions. Various techniques of injection have been described. The injection is made through the pars plana route 3mm/3.5mm from the limbus. A 27G or a 30G needle may be used for the same.

Penfold et al., 1995[17] described injection technique using 30 gauge needle through superotemporal pars plana 4.5 mm from the limbus Nelson 2003[53] described using 27 or 30 gauge needle 3.5 mm posterior to the limbus in pseudophakic eyes and 4 mm posterior in phakic eyes. Gilles 2003[18] used 27 gauge needle Danis 2003[19] used 30 gauge needle injection performed through 6 o 'clock pars plana 4 mm from the limbus.

Moshfeghi 2003[22] used 27, 29 or 30 gauge needle 3mm in pseudophakic eyes and 4 mm in phakic eyes in inferior or inferotemporal quadrant and aqueous paracentesis and tap performed when necessary. Jonas 2003[24] described using 3-3.5 mm from the limbus as the injection site and preoperative paracentesis to reduce iop. Bakri 2003[27] described a technique of using 27 gauge needle and injection performed 3.5 mm posterior to the limbus.

INDICATIONS FOR TRIAMCINOLONE ACETONIDE

1. Choroidal neovascular membrane
2. Clinically significant macular edema in diabetes mellitus
3. Macular edema in retinal vein occlusion
4. Cystoid macular edema in pseudophakia
5. Exudative retinal detachment in Vogt Koyanagi Harada syndrome
6. Sympathetic Ophthalmia
7. Idiopathic retinal vasculitis
8. Idiopathic panuveitis
9. Intermediate uveitis
10. Behcet’s disease
11. CME secondary to uveitis not responding to treatment
12. CNVM secondary to serpiginous choroiditis
13. Chronic uveitis
14. Pars planitis
15. Iris neovascularization

ADVERSE EFFECTS OF TRIAMCINOLONE ACETONIDE:[32]

Various studies were published on the therapeutic effects and adverse effects of the intravitreal administration of triamcinolone acetonide. Penfold et al., 1995 reported cataract formation as the main side effect. Gilles 2003 reported mainly ocular hypertension and cataract as the adverse effects. Bakri , Danis reported mainly ocular hypertension as the side effect of triamcinolone acetonide. Jonas et al in his meta analysis published in 2005 reported ocular hypertension as the most common complication. Endophthalmitis is one of the dreaded complications of intravitreal injection. The following studies were used in calculating the prevalence of endophthalmitis. Moshfeghi in 2003 reported 8 culture positive cases of endophthalmitis. Nelson in 2003 reported 7 cases of pseudoendophthalmitis and 2 culture positive cases[53]. Roth in 2003 reported 7 cases of pseudo endophthalmitis.

GLAUCOMA AFTER INTRAVITREAL INJECTION OF TRIAMCINOLONE ACETONIDE

A rise in intraocular pressure is one of the most common of side effects following intravitreal injection of steroids.[26] The mechanism of increase in intraocular pressure is thought to be due to increased outflow resistance induced by biochemical and morphologic changes in the trabecular meshwork. Jonas et al noted a rise in 50% of patients who were given an intravitreal injection of 25mg of triamcinolone acetonide. This rise started 1 to 2 months after the intravitreal injection.[26] IOP rises have been reported as early as 1 day following intravitreal injections. While many of these patients have only a moderate rise in IOP, some patients may have a severe rise. Bakri et al, reported a severe rise in IOP in 27.9%[27]. The time-response relationship of steroid-induced ocular hypertension has important implications in deciding the frequency of follow-up. The post injection rise in IOP is very variable and may occur at different times of follow-up. This means that unless the follow-up is frequent, this rise may well be missed.[26]

Kaushik et al, reported a higher frequency with glaucoma occurring in seven out of nine patients treated for cystoid macular edema following CRVO. One patient had glaucoma resistant to maximally tolerated medication and

required pars plana vitrectomy to remove the steroid to control the IOP.[29] Chew and associates had reported that young patients with CRVO had wide diurnal swings in IOP and were predisposed to develop steroid induced ocular hypertension. This is of concern as such a rise would further compromise retinal perfusion in these patients [54.]

Gillies in a study of intravitreal triamcinolone injected in a dose of 4mg to patients with classic neovascular age-related macular degeneration, noted a significant rise in IOP in twenty one of 75 eyes (28%), compared with one of 76 placebo-treated patients (1.31%). A severe rise of IOP occurred in only two patients. All patients achieved good control with topical medications. A single medication sufficed in eighteen of these eyes while the other three required two medications. He observed that adverse events were also noted in patients injected with triamcinolone acetonide injected into the posterior subtenon's space which by far is considered to be the safest route of injection with IOP rise occurring in 30% of patients.[18]

Antcliff used an injection of 2mg of triamcinolone acetonide in six patients with cystoid macular edema secondary to uveitis resistant to other routes of steroid administration and cyclosporine A. Patient 2 who had CME initially responsive to systemic steroids developed a rise in intraocular pressure starting one week after injection. The pressure rose to 40mmHg and

was resistant to topical and systemic medications and underwent an uneventful trabeculectomy. The trabecular meshwork showed necrotic tissue with no deposition of triamcinolone acetonide on histopathological examination. The raise in IOP may not be associated with the dose used[11].

Suggested mechanisms of the corticosteroid induced increase in intraocular pressure:[55]

Corticosteroids are believed to decrease outflow by inhibiting degradation of extra cellular matrix material in the trabecular meshwork (TM), leading to aggregation of an excessive amount of the material within the outflow channels and a subsequent increase in outflow resistance two patterns of extra cellular deposition have been described in the TM of Steroid-induced glaucoma patients; fingerprint-like deposition of material in the uveal meshwork, and accumulation of fine fibrillar material in the juxtacanalicular region. The response might be due to an alteration of the metabolism of mucopolysaccharides, leading to their accumulation in the TM. It was proposed that corticosteroids, which stabilise lysosomal membranes, could reduce the release of lysosomal hyaluronidase, this resulting in a relative inhibition of hyaluronate depolymerisation. The subsequent accumulation of mucopolysaccharides could, it was suggested, cause retention of water (‘biological edema’) and subsequent narrowing of the trabecular spaces.

Support for a steroid-induced effect within the outflow. Channels have come from animal studies, experiments with cultured human TM cells and perfusion-cultured donor eye models.

In rabbit eyes glucocorticosteroid receptor concentration has been shown to be high in ocular tissue and intravenously administered steroid has been

found to bind specifically to the nuclei of cells in the outflow channels in a similar manner to the binding of Dexamethasone reported to occur in cultured human TM cells Glucocorticocoids have been shown to alter TM cell morphology by causing an increase in nuclear size and DNA content A further study has shown that steroids also induce proliferation and activation of the endoplasmic reticulum, Golgi apparatus, and increase deposition of extra cellular matrix material. The amounts of glycosaminoglycans, elastin and fibronectin have been shown to increase in tissue culture preparations in response to dexamethasone treatment while the levels of tissue plasminogen activator, stromelysin, and the activity of several TM metalloproteases have been shown to fall. Furthermore, excessive accumulation of glycosaminoglycans has been identified in human trabecular meshwork specimens obtained from steroid responders

In support of the evidence for extra cellular matrix deposition, dexamethasone treatment has also been shown to inhibit TM cell arachadonic acid metabolism and reduce phagocytic activity TM cells have phagocytic properties, the function of which is to clear the outflow channels of debris. A steroid-induced inhibition of phagocytosis within the meshwork could result in accumulation of channel debris and decreased facility of outflow so contributing to steroid-induced Glaucoma. Structural changes in the TM cells have also been proposed.

Clark et al[60] discovered that dexamethasone caused cross-linkage of actin fibres leading to the formation of networks within cultured human TM cells. The actin network structure was reversible following cessation of corticosteroid administration to the human TM cultures. It was suggested that the response might be mediated by the TM glucocorticoid receptor. However, the effect of such an alteration of cellular cytoskeleton on TM cell function remains unclear.

Clark et al[56] went on to demonstrate histological and pressure changes in steroid treated, perfusion-cultured human eyes. IOP was measured using a pressure transducer within the eye, so that the measurement was not affected by corneal thickness. In those eyes in which there was a pressure increase, morphological changes included thickened trabecular beams, decreased

Intertrabecular spaces, thickened juxtacanalicular tissues, and increased amounts of amorphous granular extra cellular material. In another perfusion-cultured human eye model glycosaminoglycans deposition in the meshwork increased with increasing duration of steroid exposure.

It is hoped that recent advances in novel molecular genetic methods will allow a better understanding of the mechanisms causing the steroid-induced glaucoma. By gene deletion or over expression studies, the exact role of individual genes responsible for the modulation of meshwork extra cellular material may be identified in the near future.

MANAGEMENT OF CORTICOSTEROID-INDUCED GLAUCOMA

Monitoring of IOP

A baseline measurement of IOP should be taken prior to commencement of corticosteroid therapy. Increase in intraocular pressure occurs transiently and gets controlled once the drug is stopped in case of topical medication. In case of subtenon's and intravitreal administration the rise occurs slowly and persists for a long time hence monitoring of lop is mandatory in these patients.

In about 3% of cases and in particular when there is a family history of glaucoma and/or chronic use of steroid, the ocular hypertensive response has been shown to be irreversible. The management of such cases is no different from that for POAG.

Medical anti glaucomatous therapy
Beta-blockers

Topical beta-blockers can be used to control corticosteroid-induced glaucoma, preferably following cessation of steroid therapy and are a popular first-line agent for the condition.

Prostaglandin analogues

Concomitant latanoprost has been shown to be as effective as cessation of therapy in controlling the IOP rise associated with corticosteroids so can be useful if steroid treatment must be continued. However, latanoprost has been reported to induce Uveitis and is relatively contraindicated in eyes with uveitic glaucoma. Latanoprost has been shown to cause cystoid macular edema in certain pseudophakic eyes in the early postoperative period (when steroids are likely to have been prescribed. So caution should be exercised when prescribing prostaglandin analogues in such eyes.

Alpha agonists

Brimonidine can be useful in many patients with steroid-induced glaucoma, although there have been reports of Brimonidine-induced uveitis in a minority of patients

Carbonic Anhydrase Inhibitors :

Oral acetazolamide is an effective short-term treatment for the control of IOP in all forms of glaucoma, including that induced by corticosteroids. Over longer periods, the side effect profile of acetazolamide tends to make it poorly tolerated and it is contraindicated in certain patients, such as those with renal impairment. However, topical carbonic anhydrase inhibitors

(dorzolamide and brinzolamide) are of use in the control of IOP due to corticosteroid induced Glaucoma.

Argon Laser Trabeculoplasty (ALT)

Jonas et al [57,58]has suggested ALT as one standard procedure for controlling intravitreal induced ocular hypertension.

Filtration surgery[59]

Trabeculectomy remains an effective treatment for glaucoma in those patients who have a persistently raised IOP following cessation of corticosteroid therapy and are refractory to medical therapy. However, as always, the adverse consequences of trabeculectomy or other forms of drainage surgery should be considered in relation to the potential benefits. It seems unlikely that a steroid response occurs following successful filtration surgery. If one wants to maintain the positive therapeutic effect of triamcinolone acetonide and if, simultaneously, one has to treat IOP elevation, filtering surgery may be a good option. According to previous small case series studies, filtering surgery in eyes with intravitreal triamcinolone acetonide may have a positive surgical and functional outcome and still leaves the triamcinolone acetonide in the eye One has to take into account, however, that after filtering surgery the duration of the intraocular availability of

triamcinolone acetonide may be reduced due to a possibly higher turnover rate.

Pars Plana Vitrectomy[60]:

PPV may be another treatment option considering that the cause of rise in IOP is the persistence of tricort depot. The removal of triamcinolone acetonide will be combined with the disadvantage that the beneficial effect of intravitreal triamcinolone acetonide will soon be terminated after the PPV. A therapeutic advantage of a pars plana approach may be the relief of vitreoretinal traction on the macula, which may lead to a decrease in macular edema in patients with diabetic macular edema and epiretinal membranes This advantage must be compared with the surgical risk of PPV.In the future, subtenon anecortave acetate may play a role in the treatment of triamcinolone acetonide–induced ocular hypertension, because it has been said that anecortave acetate may be able to reverse steroid-induced ocular hypertension (Robin A, personal communication, 2005).

AIMS AND OBJECTIVES

To study the effect of intravitreal triamcinolone on intraocular pressure in eyes with no preexisting evidence of glaucoma.

INCLUSION CRITERIA:

Patients with progressive decrease in visual acuity due to

1. Exudative age related macular degeneration with subfoveal neovascularisation
2. Diffuse diabetic macular edema
3. Macular edema due to central retinal vein occlusion, branch retinal vein occlusion.
4. Cystoid macular edema following cataract surgery.
5. Macular edema following laser treatment.

EXCLUSION CRITERIA:

Patients with pre existing glaucoma and others like irregular cornea.

MATERIALS AND METHOD

It was a prospective consecutive non comparative interventional case series study conducted in Aravind eye hospital and includes all patients with diffuse diabetic macular edema, cystoid macular edema following cataract surgery, macular edema due to central retinal vein occlusion ,branch retinal vein occlusion, macular edema following laser treatment, exudative age related macular degeneration with sub foveal neovascularisation.

Treatment was with intravitreal triamcinolone acetonide after obtaining informed consent from all the patients. Intraocular pressure measured before the procedure and after the procedure and at one month, three months and six months by Goldman applanation tonometer.

All the patients had undergone comprehensive ophthalmic workup including testing visual acuity, baseline intraocular pressure measurement by Goldmann applanation tonometer, slit lamp evaluation gonioscopy and indirect ophthalmoscopy.

Other investigations like FFA, OCT were done in majority of our patients to document macular thickness and patients had undergone evaluation for their systemic illnesses.

Treatment:

The procedure of intravitreal triamcinolone acetonide injection was performed in operation theatre under aseptic conditions. The eyes were prepared with topical anesthetic agent (paracaine), painted with povidone Iodine cleaned and draped. 0.1 ml containing 4 mg of commercially available triamcinolone acetonide was injected into the vitreous cavity using 26 gauge needle through pars plana 3 mm from the limbus in case of aphakia, 3.5 mm in pseudophakia, 4 mm in phakic eyes.

At the end of procedure optic nerve head perfusion and central retinal artery pulsation were checked with indirect ophthalmoscopy and intraocular pressure digitally. In case of digitally raised intraocular pressure and/or presence of central artery pulsation paracentesis done to reduce intraocular pressure. Sterile pad and bandage applied at the end of procedure.

The patients were reviewed on the same day evening and they were subjected to slit lamp evaluation for presence of tricort crystals and intraocular pressure was measured using Goldmann applanation tonometer. In case of elevated intraocular pressure the patients were evaluated in our glaucoma clinic. The patients without rise in intraocular pressure were advised to use antibiotic eye drops for one week and advised to review after one month.

Follow up:

Our patients were regularly followed up in retina clinic at 1 month, 3 months and 6 months. In each visit patients underwent vision testing, intraocular measurement using Goldmann applanation tonometer, slit lamp evaluation and indirect ophthalmoscopy. FFA and OCT were advised in their follow up visits to document macular thickness and done in patients who were willing to undergo these investigations. Those patients with increased intraocular pressure were followed up in glaucoma clinic also. The above data were entered in standard form and transferred to an electronic database and subsequently analyzed.

Data collection and outcomes:

Patients were seen at one, three, six months and data on intraocular pressure and management of increased intraocular pressure were entered on to the standard data collection form and transferred on to an electronic data base.

This case series study included 94 eyes of 94 patients of which 59 were males and 35 were females. Mean age of the study group was 58.03 years (Standard deviation (S.D) = 11.67) .Among these 94 patients 12(12.8%) were less than or equal to 45 years.27 were in the age group of 46-55 (28.7%).

30 were in the age group of 56-65 (31.9%).25 (26.6%) were in the age group of more than or equal to 66 years.

81.5% (n=53) of cases had diabetic mellitus, 41.5% (n=27) had hypertension, 7.75 (n=50) had renal disease, 6.2% (n=40) had cardiac disease. All these patients received 4 mg of triamcinolone acetonide as a treatment for diabetic macular edema in 29 patients (30.9%), 22 patients for central retinal vein occlusion (23.4%), 32 patients for exudative macular edema (34%), 6 patients for post operative cystoid macular edema (6.4%), and 5 patients for branch retinal vein occlusion (5.3%).

All the patients were fully informed about the experimental nature of the treatment and all the patients had signed an informed consent. In this study none of the patients had primary open angle glaucoma, chronic closed angle glaucoma or ocular hypertension.

All the patients received an intravitreal injection of 4 mg of triamcinolone acetonide as previously described. None of the eyes received steroids either topically or systemically following treatment.

At the baseline of the study intraocular pressure the mean baseline being 15.03 ± 2.989 mm Hg, the range being 10 -20 mm Hg. If the intraocular pressure exceeded 21 mm Hg topical beta blockers and/or carbonic anhydrase

inhibitors were started as the medication of first choice. If the initial intraocular pressure was very high then combination of both were started. Filtering surgery was indicated if intraocular pressure continued to be higher despite maximal medical therapy and development of glaucomatous optic neuropathy.

RESULTS

In the study group mean intraocular pressure increased significantly (p=0.000) after the intravitreal triamcinolone injection from 15.03 ± 2.989 mm Hg to 23.65 ± 11.226 mm Hg, during follow up. The mean rise in intraocular pressure was 8.62 ± 10.647 mm Hg, with the proportion increase being 59.03%

Rise in intraocular pressure is defined as measurements outside the normal range at least one IOP measurement higher than 21 mm Hg. Increased IOP was observed in 31 patients in this series. Increase in IOP is defined as the difference between maximal postoperative IOP and baseline IOP. Mean increase in IOP for the entire study group was 8.62 ± 10.647 mm Hg.

The entire study group is divided into two subgroups as triamcinolone responders and triamcinolone non responders. Predictive factors for increased IOP were analyzed. The subgroups did not vary significantly in gender (p=0.508). Ocular condition for which intravitreal triamcinolone was administered was analyzed. The mean IOP increased significantly (p=0.024) in case of diabetic macular edema. Among the systemic condition diabetes

mellitus showed a significant association (p=0.045) though logistic regression failed to prove a significant correlation with either of the two.

The mean maximal IOP vary significantly with the mean baseline iop (p=0.000).Among the triamcinolone responders the mean baseline IOP was 15.71 ± 2.912 mm Hg, and the mean maximal IOP was 36.74 ± 10.689 mm Hg with the proportion increase being 136.94%.

Of the 94 patients, 31 showed increased intraocular pressure following treatment with intravitreal triamcinolone.71% of the triamcinolone responders had a baseline IOP of greater than or equal to 15mm Hg and 29% had base line IOP less than 15 mm Hg. Among the triamcinolone non responders 46% had IOP greater than or equal to 15mm Hg and 54% had IOP less than 15 mm Hg. Overall the baseline IOP showed a positive correlation with the increase in IOP (P=0.01) and the risk of increased IOP is 2.06 times more for the patients with the baseline IOP greater than or equal to 15 mmHg than the patients with the base line IOP of less than 15 mm Hg.

The mean time of increase in IOP is 2.9 ± 1.921 months. Mean IOP at the end of 6 months being 24 ± 13.14 mm Hg. Increase in IOP was observed in the immediate post treatment period in 8.3% of patients in less than or equal to 45 years age group, 11.1% in 45-55 years age group, 23.3% in 56-65 years

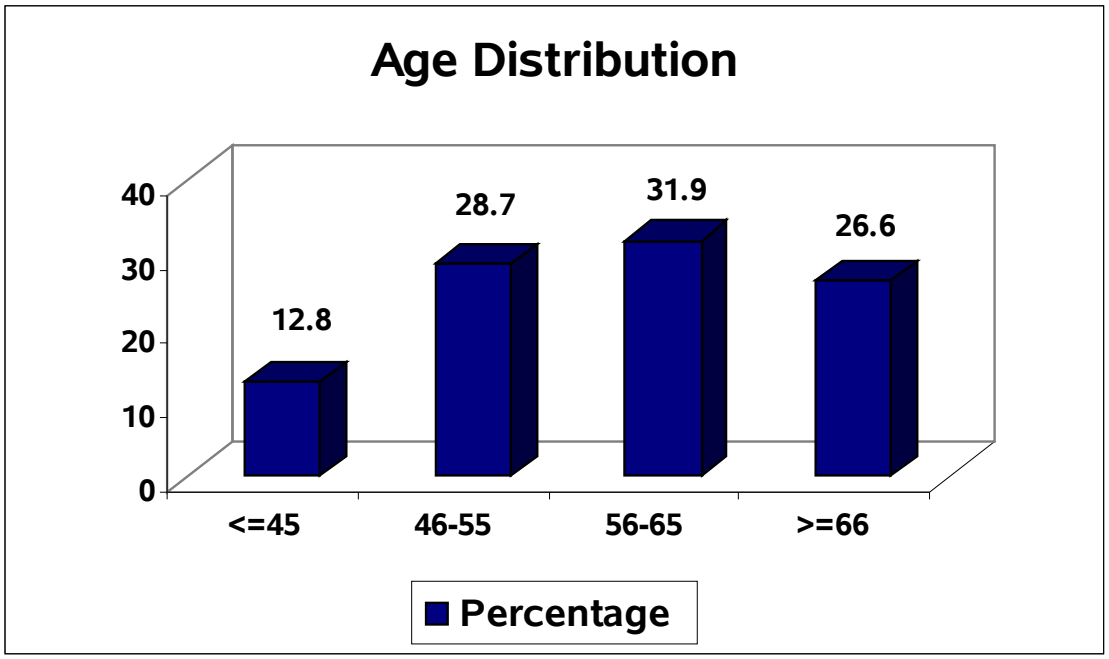
age group and none in more than 66 years age group. Follow up at one month showed 40% of patients in less than or equal to 45 years age group had increase in IOP, 25.9% of 46-55 years , 30% of 56 -65 years age group and 8% of more than 66 years age group. Follow up at 3 months showed that 50% of patients in less than or equal to 45 years had increase in IOP , 22.2% in 46-55 years age group, 28.6% in 56-65 years age group. Follow up at 6 months showed that 30% had increase in IOP in less than or equal to 45 years ,8% in 46 -55 years age group 25% in 56-65 years and 5% in more than 66years age group. The increase in IOP tend to occur more in younger age group and it persisted for a longer period (p=0.005). Incidence of increased IOP in first month was 23.9%, third month was 6.9% and sixth month was 3.6%

31 of 94 patients had increase in IOP in this study (33%). Out of 31 patients 8 were treated initially with combination therapy (25.80%) and 23 patients received monotherapy (74.12%) within 6 months of study period. 45% were successfully treated with medications and discontinued medications.45 % required medications at the end of 6 months to keep IOP under control. One patient underwent trabeculectomy (3.225%) and 2 patients required anterior retinal cryopexy (6.45%).

TABLES AND FIGURES

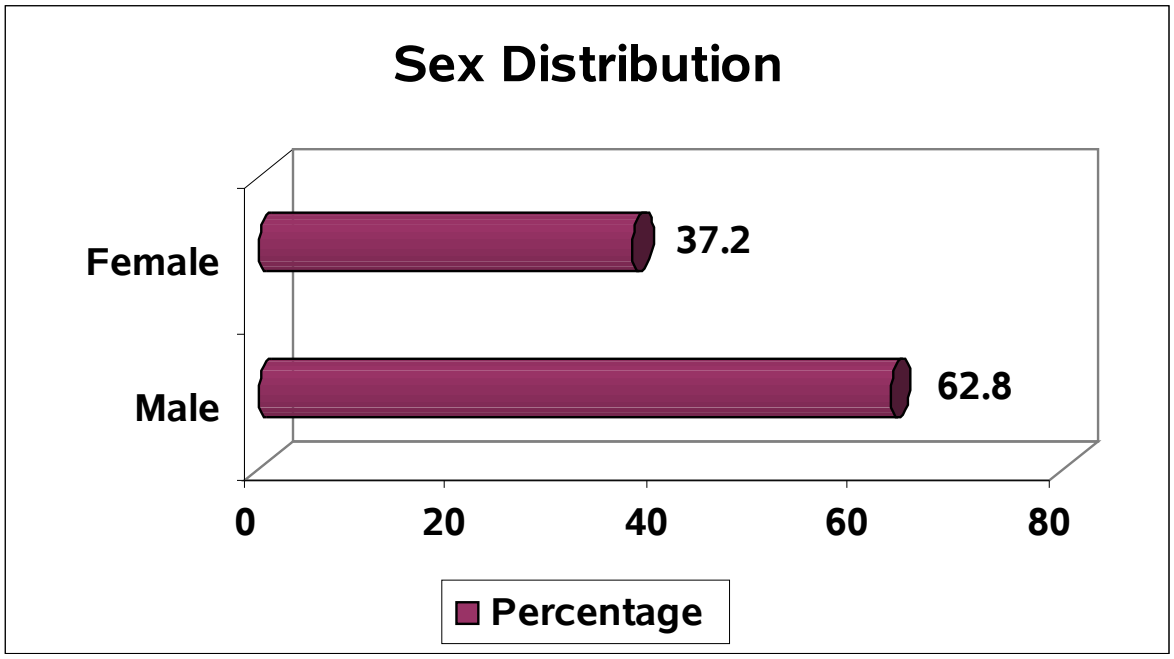
AGE

	Frequency	Percent
< = 45	12	12.8
46-55	27	28.7
56-65	30	31.9
> = 66	25	26.6
Total	**94**	**100.00**



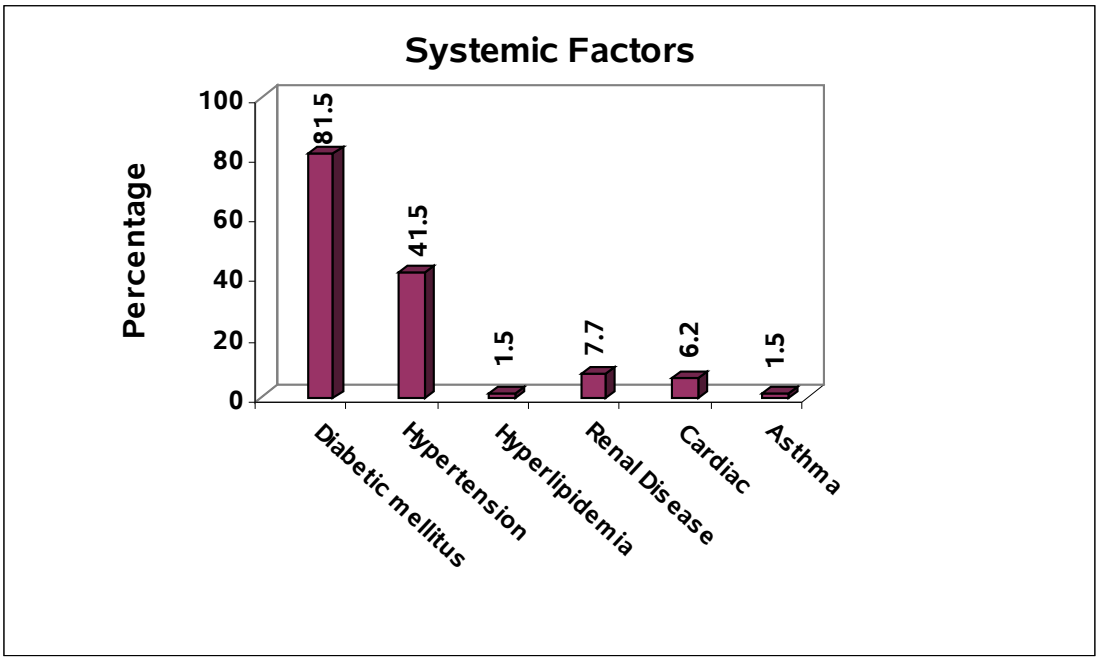
SEX

	Frequency	Percent
Male	59	62.8
Female	35	37.2
Total	94	100.0



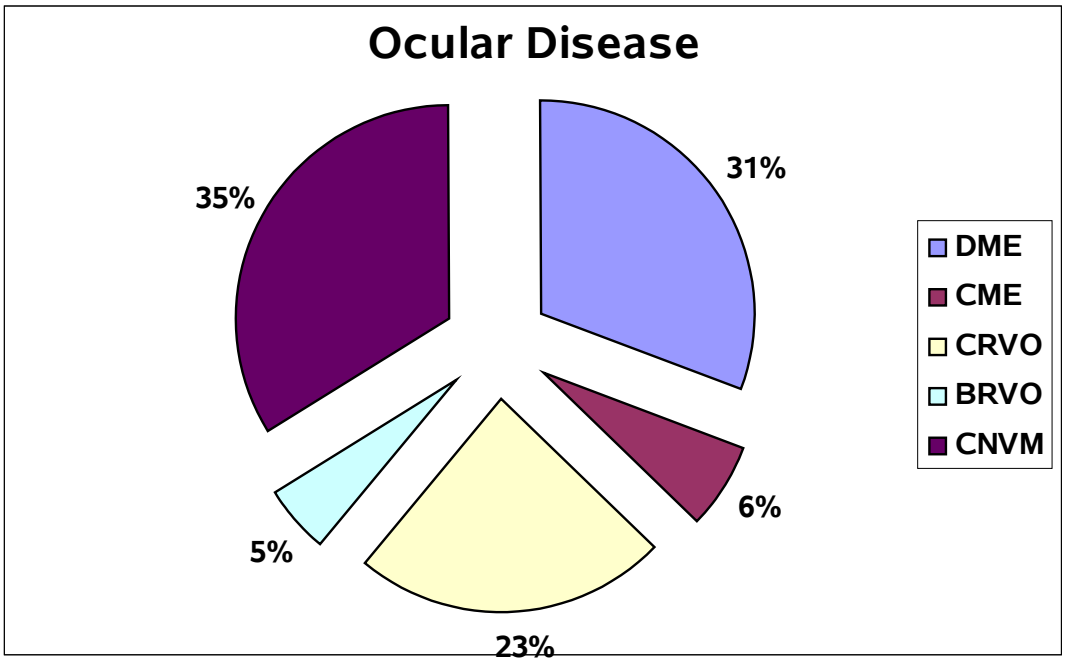
SYSTEMIC DISEASE

	Count	Percentage
Diabetic Mellitus	53	81.5
Hypertension	27	41.5
Hyperlipidemia	1	1.5
Renal disease	5	7.7
Cardiac	4	6.2
Asthma	1	1.5



OCULAR DISEASE

	Frequency	Percent
DME	29	30.9
C ME	6	6.4
CRVO	22	23.4
BRVO	5	5.3
CNVM	32	34.0
Total	**94**	**100.0**



Descriptive Statistics on Age for the entire study group (in years)

	N	Range	Minimum	Maximum	Mean	Std.Deviation
Age	94	55	27	82	58.03	11.693

Descriptive Statistics on Baseline IOP for the entire study group

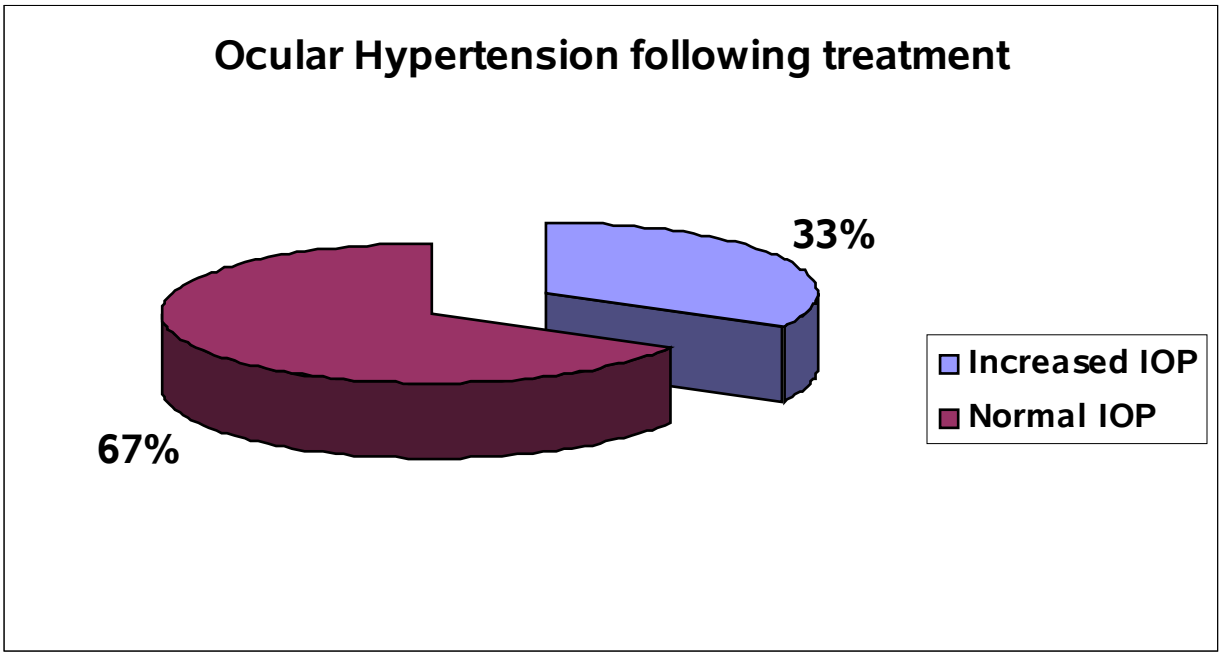
(in mm Hg)

	N	Range	Minimum	Maximum	Mean	Std.Deviation
Baseline IOP	94	10	10	20	15.03	2.989

Descriptive Statistics on Characteristics of IOP for the entire study group

following treatment

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Baseline IOP	94	10	10	20	15.03	2.989
IOP range	94	62	12	74	23.65	11.226
Last follow up IOP	94	64	10	74	18.03	8.922
Time of IOP rise (in months)	94	5	1	6	2.72	1.750
Proportion Increase (%)	94	282.50	-12.50	270.00	50.0362	67.340
Amount of IOP rise	94	56	-2	54	8.62	10.647

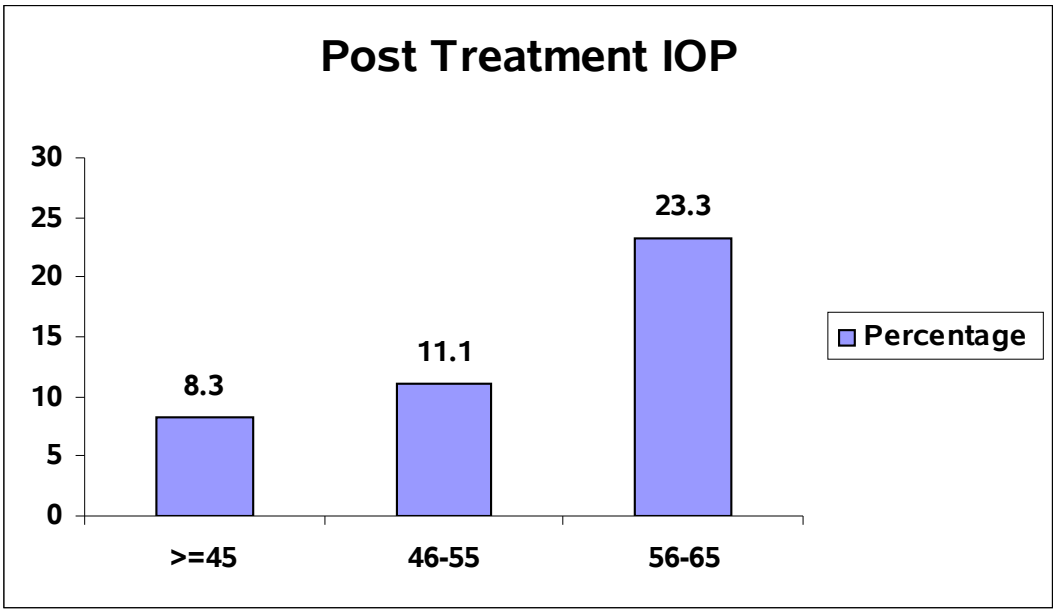


OCULAR HYPERTENSION FOLLOWING TREATMENT

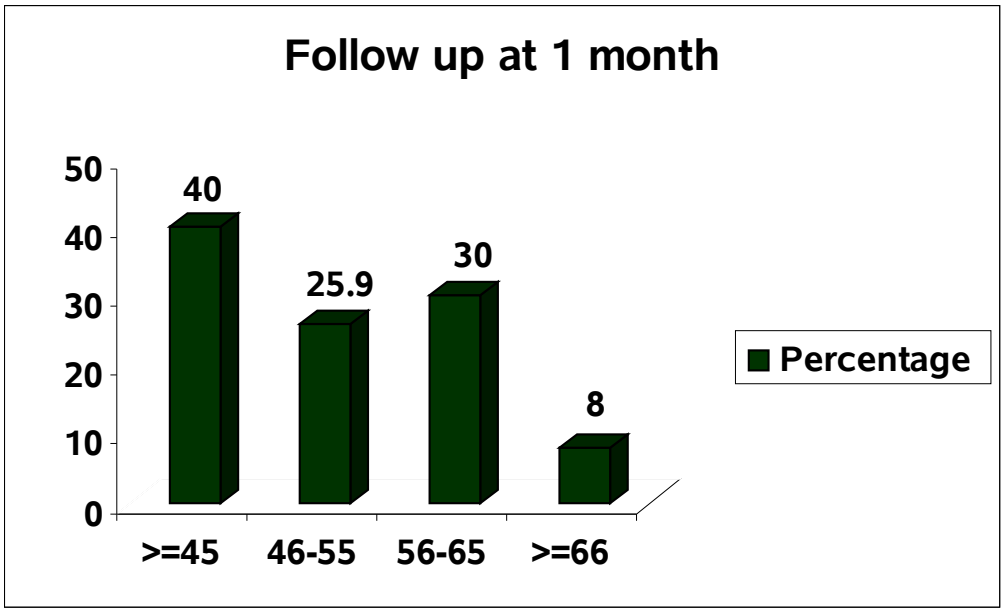
	Frequency	Percent
Increase in IOP	31	33.0
No increase in IOP	63	67.0
Total	**94**	**100.0**

Descriptive Statistics on Characteristics of IOP for triamcinolone responders

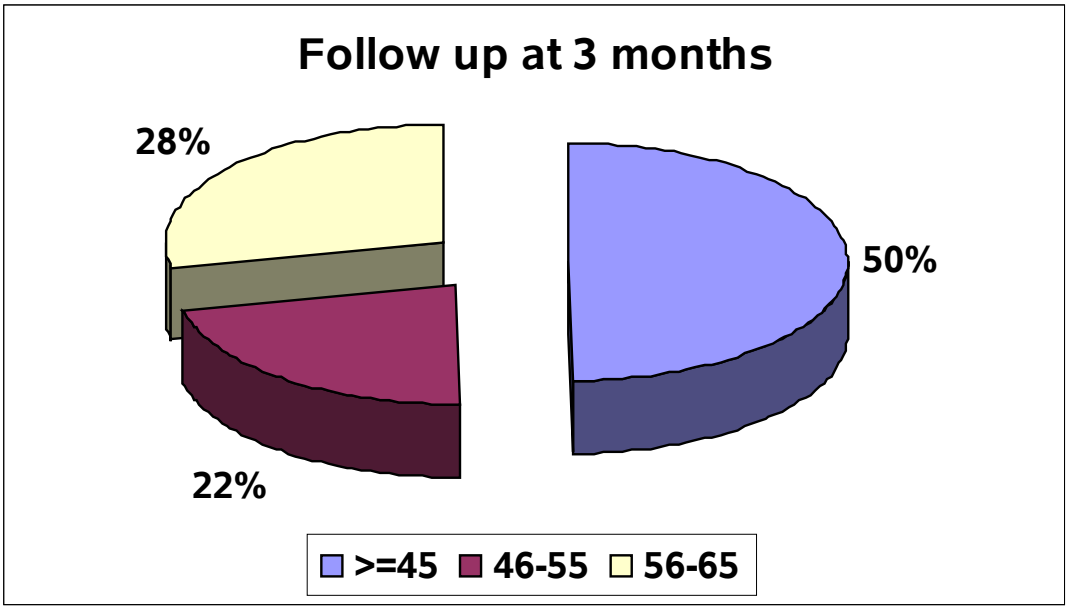
	N	Range	Minimum	Maximum	Mean	Std. Deviation
Baseline IOP	31	10	10	20	15.71	2.912
IOP range	31	52	22	74	36.74	10.689
Last follow up IOP	31	63	11	74	24.00	13.148
Time of IOP rise (in months)	31	5	1	6	2.90	1.921
Proportion Increase (%)	31	220.00	50.00	270.00	136.96	57.68
Amount of IOP rise	31	46	8	54	21.03	9.731



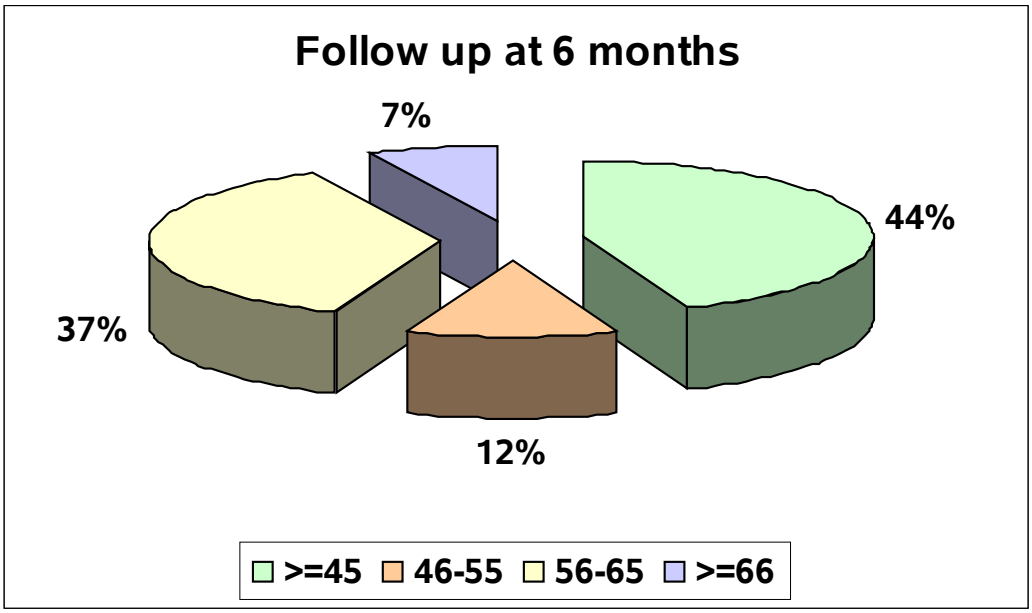
Increase in IOP was observed in the immediate post treatment period in 8.3% of patients in less than or equal to 45 years age group, 11.1% in 45-55 years age group, 23.3% in 56-65 years age group and none in more than 66 years age group.



Follow up at one month showed 40% of patients in less than or equal to 45 years age group, 25.9% of 46-55 years , 30% of 56 -65 years age group and 8% of older than 66 years age group had increase in IOP

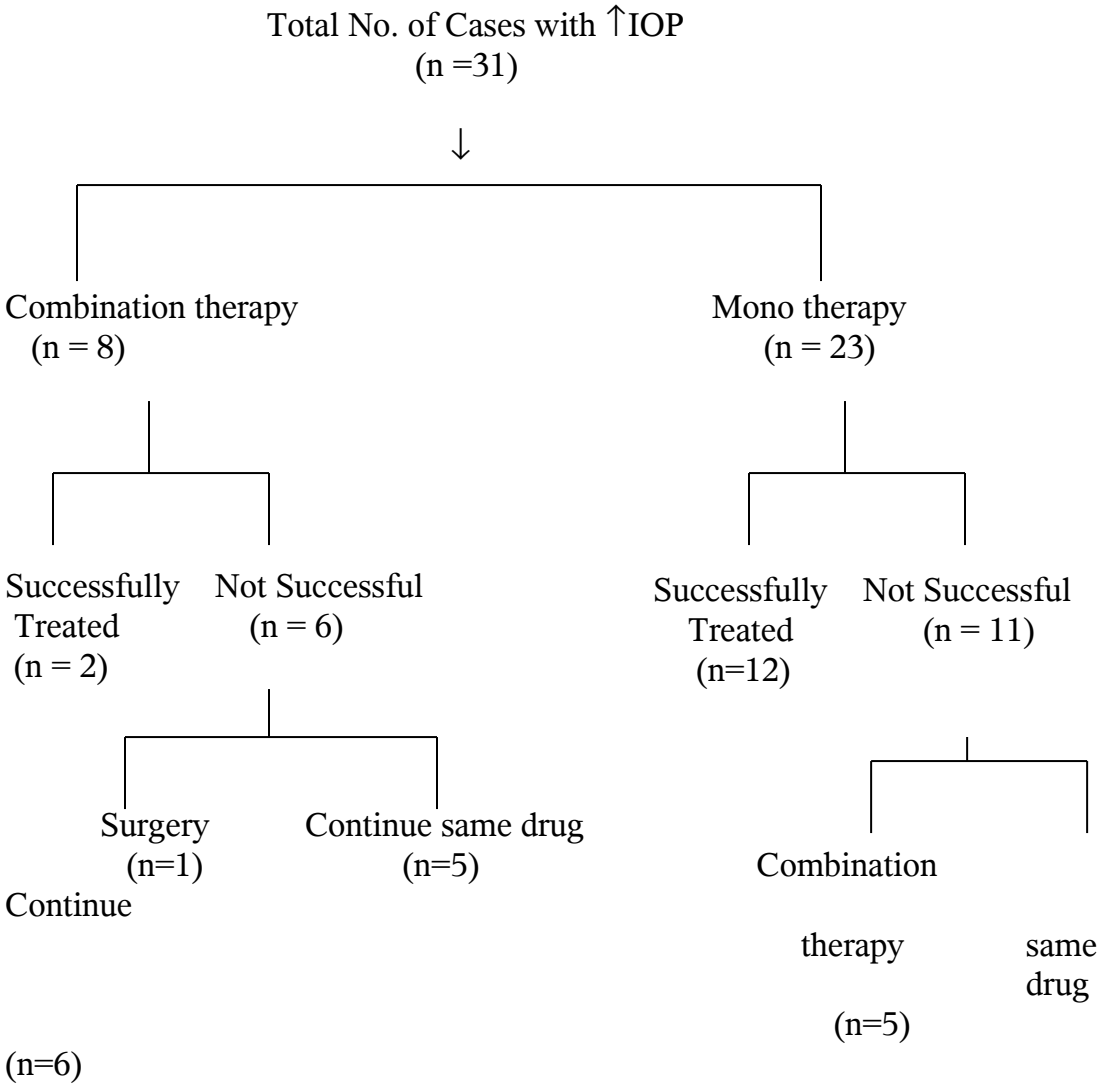


Follow up at 3 months showed that 50% of patients in less than or equal to 45 years , 22.2% in 46-55 years age group, 28.6% in 56-65 years age group had increase in IOP



Follow up at 6 months showed that 30% in less than or equal to 45 years, 8% in 46 -55 years age group, 25% in 56-65 years and 5% in more than 66years age group had increase in IOP

MANAGEMENT OF INCREASED IOP



DISCUSSION

The aim of this study was to analyze the effects of intravitreal triamcinolone on IOP and to find out the baseline characteristics that can cause increase in IOP.

Variables that were analyzed in this study included age gender systemic disease, ocular condition for which the drug was administered, baseline IOP.

Age proved to be an important determinant in the development of increased intraocular pressure ($p=0.005$) increased IOP tend to occur in younger age group than the older age group and persists for a longer time. At the end of one month follow up 40% of the patients aged less than or equal to 45 years showed an increase in IOP. At the end of 3 months 50% had increase in IOP, and at 6 months 30% had increase in IOP. The mean age of triamcinolone responders in other studies were relatively high compared to this study group. Though Jonas et al., found a tendency of increased IOP in younger age group their mean age of triamcinolone responders was 71.3 ± 9.9 years which was very high compared to this study. Smithen et al., did not find any correlation with age.

Increase in intraocular pressure did not show any variation with gender. Though increased IOP showed significant variation with regard to diabetes mellitus and diabetic macular edema logistic regression failed to show any positive correlation .So diabetes might not be a contraindication for intravitreal injection which was proved in other studies also.

Increase in IOP showed a positive correlation with the base line IOP. Patients who had higher baseline IOP tend to have increased incidence of intraocular pressure elevation (relative risk being 2.06 and p value 0.023).The mean time of IOP rise occurred in 2.9±1.921 months. The incidence of ocular hypertension was highest in 1st month (23.9%) in 3rd month was 6.9% and in 6th month being 3.6%

90% of the patients did not have progressive optic nerve head damage and IOP was controlled by medical measures alone. One out of 31 patients required trabeculectomy because of progressive optic nerve head damage and two required ARC for retinal neovascularisation.

STRENGH OF THE STUDY:

- Prospective study.
- 4mg of triamcinolone acetonide was used
- None of the cases had repeat injection during the study period.

- None of the cases had glaucoma at the baseline
- Only one eye of a single patient was included in the study.

LIMITATIONS OF THE STUDY:

1. **Small sample size**.

Though there was significant variation with age and occurrence of increased IOP, since the no. of patients were very less the results could not be generalized and further studies are required to determine the age limit for intravitreal triamcinolone acetonide.

2. **Baseline IOP**

Since baseline IOP was determined on a single measurement taken by different persons at different time of time of the day which might not reflect the true baseline IOP.

3. **Follow up period**

Follow up period was 6 months while intravitreal triamcinolone might persist in the eye for more than 9 months.

CONCLUSION

A prospective study on 94 eyes after the administration of a single dose of intravitreal triamcinolone acetonide showed that

1. Incidence of IOP elevation was 33%
2. Mean time of increase of IOP was 2.9 months.
3. Incidence of ocular hypertension in 1st month was 24%
4. Age and baseline IOP could be the positive predictive factors.
5. 90% of the cases were controlled with medical therapy.

IOP elevation was transient and 90% of cases did not have optic nerve head changes and elevated IOP was controlled with medications.

PROFORMA

EFFECTS OF INTRAVITREAL TRIAMCINOLONE ON INTRAOCULAR PRESSURE

PATIENT INFORMATION:

a. Name:

b. Age :

c. Sex : ☐ Male ☐ Female

d. MR.No : _____ Serial no: _____

SYSTEMIC DISORDERS:

a. Diabetic mellitus :

b. Hypertension :

c. Hyperlipidemia :

d. Renal disease :

e. Others : (if any specify)

FAMILY HISTORY OF GLAUCOMA :

PAST HISTORY OF INCREASED IOP DUE TO TOPICAL STEROIDS:

OCULAR CONDITION FOR WHICH INTRAVITREAL TRICORT GIVEN:

a. Diabetic macular edema :
b. Cystoid macular edema :
c. Macular edema due to
CRVO :
BRVO :
d. CNVM :

DETAILS OF EXAMINATION:

a. Visual acuity : RE
LE

b. Best corrected visual acuity : RE
LE

c. Intraocular pressure : RE
LE

d. Fundus examination:

	RE	LE
1. Disc:		
CDR		
NRR		
RFNL		
2. Vessels:		
3. Macula:		

DATE OF ADMINISTRATION OF TRICORT:

POST TREATMENT IOP:

Effects of Intravitreal Triamcinolone on Intraocular pressure

Indication for Triamcinolone Use:

1. Episode

☐ 1 month ☐ 3 month ☐ 6 months

2. Baseline Intraocular Pressure

Right eye mmHg Left eye mmHg

3A.Study eye

3A.Intraocular pressure at follow up

	1 month	3 months	6 months
Right eye			
Left eye			

3B.Visual acuity:

	1 Month	3 months	6 months
Right eye			
Left eye			

4. Medication Started:

☐ Yes ☐ No

(i) If Yes: A. Strength B. Frequency C Date Initiated

1. Timolol 0.25% 0.5%

☐ ☐

2. Brimonidine 0.2% 0.15%

(ii) Four weeks follow-up
IOP under control

→ Success- continue till 6 months follow up

IOP Drop not satisfactory

Substitute:
Week 4 : …….
…….
Week 8 : …….
…….
……..

No IOP drop

Add:
Week 4: …….
……..
……....
Week 8: …….
…….
……...

(iii) IOP drop not adequate with medications

→ Consider trabeculectomy

a) With Mitomycin C
b) Without Mitomycin C

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